Learning to Use a New Drug—the Fast-acting Insulin Analogues

It has been said, not entirely in jest, that were insulin to be discovered today, it would probably not get a licence. Insulin therapy must certainly be one of the most difficult drug regimens for a patient to handle. And yet insulin, as a natural product, should—and in one sense does—have one of the best safety profiles on the market. Its only major side-effect is technically an overdosage—hypoglycaemia.

Exogenous insulin is not under endogenous control, enters the circulation by the wrong route and, in its currently available forms, has pharmacokinetics that are far from physiological. Until recently, even our shortest, fastest acting insulins were slower in onset and longer in duration of action than the prandial peaks of endogenous insulin, resulting in unreasonable demands that patients decide and administer a dose up to 60 minutes before they need it and then snack within 3 hours of finishing the related meal.[1] Failure to achieve such a demanding regimen risks either post-prandial hyperglycaemia and poor control or pre-prandial hypoglycaemia and, by another definition, even worse control.

The insulin analogues were designed to have pharmacokinetics that more closely resembled the physiological pancreatic insulin response to a meal. The first to reach the market, Lys(B28), Pro(B29) human insulin, *aka* Humalog, has a quicker onset, faster peak and shorter duration of action after subcutaneous injection than conventional soluble insulins because the reversal of two amino acids in the β chain diminishes the tendency of the insulin molecules to aggregate. Smaller molecules are absorbed faster. Suddenly we have an insulin that not only can but should be given immediately before food, significantly reducing guilt burdens for patients, and even, possibly, could be given to children after they had finally and unpredictably agreed to eat a disputed meal.[2] (Humalog has just been cleared for use in children in whom there is a specific indication.)

But is the new insulin any better than that which had gone before? Initial reports were disappointing, with no real improvements in glycated haemoglobin or hypoglycaemia rates. Then it became apparent that this was not just another insulin. It was a new drug and we needed—probably still do need—to learn how to use it.

One hypothesis for the lack of improved glucose control was that the new insulin reduced immediate post-prandial glucose concentrations (rapid onset and peak) but encouraged hyperglycaemia just before the next meal (short duration). There are good data to suggest that this happens[3] and there were new calls for a better 'basal' insulin preparation.[4] Several strategies have been applied to improve basal insulinisation meanwhile with conventional insulins—Del Sindaco and colleagues report on one such strategy in this month's issue.[5] Combining Humalog with a small dose of an intermediate acting insulin achieved a modest improvement in glycaemic control in their patients (who were already well controlled by conventional definitions—and conventional insulins!), with no increase in hypoglycaemia. Note that trying to achieve normoglycaemia with pre-meal Humalog alone was associated with increased hypogly- caemia. Italian patients may of course be particularly prone to 'pre-prandial glucose escape' because of the relatively long times between their meals, but it is certainly not unique to them. The problem of course is the inconvenience of mixing insulins before each meal and we await with interest the development of an analogue that can be pre-mixed with NPH insulin without losing its favourable profile and the development of a pharmaceutical company with the vision to create a mix that is predominantly short acting.

Once the disadvantages of Humalog's action profile became apparent, people were fast to suggest the abandonment of the between-meal snack. Certainly this would be a welcome move for patients, forced to eat (or suffer guilt and perhaps hypoglycaemia) by prescription not by desire. This author is not aware of any evidence to suggest that this is a safe or appropriate strategy, as pre-prandial escape is more to do with dissipation of insulin than excess food ingestion. Indeed, in the clinical trials, patients on Humalog who initially did reduce snacking appeared to return to it as time went by. The study of Ronnemaa and Viikari is therefore particularly welcome.[6] While it should be noted that the snack was not eliminated in their protocol, they offer encouraging evidence that it can, with benefit, be reduced. Further work needs to be done in both these areas and *Diabetic Medicine* is pleased to be able to offer these important early studies.

Nocturnal hypoglycaemia remains a major fear for insulin users and recent studies have highlighted how common the problem may be. Classically, hypoglycaemia in the early hours of the morning has been attributed to the evening intermediate acting insulin peak, and strategies to administer the insulin as late as possible have had some success. In a recent paper in *Diabetologia*, Kanc and colleagues showed a potential reduction in nocturnal hypoglycaemia by replacing the peak-trough action of intermediate acting insulin with a steady subcutaneous infusion.[7] There is beginning to be evidence, however, that Humalog, replacing the pre-evening meal insulin, may be associated with reduced nocturnal hypoglycaemia.[8] Not

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only does this offer a potential therapeutic option, it also tells us that the pre-evening meal soluble insulin may contribute more to hypoglycaemia 8 hours later than we had previously believed. Bring back the bedtime snack and the slightly high pre-bed blood glucose goal—all is forgiven!

The new insulin analogues have not solved the problems of prandial insulin replacement for diabetic patients. Furthermore, they remain new drugs and should be approached with caution—particularly in the young. After all, we know what 50 years of conventional insulin treatment can do—more or less. There remains a risk of unexpected problems with any new agent and we should remember that the structure of the new insulin is a little closer to IGF structure than the old. This author is still of the opinion that we need to learn how best to use insulins such as Humalog and is currently recommending it only where there seems a potential clinical benefit to be gained—or where a patient is particularly keen to try. But if we can reduce hypoglycaemia risk—or the need for unwanted food intake—for patients struggling to achieve a normal lifespan and lifestyle, we should and we welcome the developing database that will eventually show us how best to use the new weapons in our armamentarium.

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